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ORAL INSULIN: BREAKTHROUGH INNOVATION AT BIOCON

Nita Sachan, Prasad Kaipa, Anand Nandkumar and Charles Dhanaraj wrote this case solely to provide material for class discussion. The authors do not intend to illustrate either effective or ineffective handling of a managerial situation. The authors may have disguised certain names and other identifying information to protect confidentiality.

It has been my dream to make a global impact with a "Made in India" label. I think a lot of my generation comes from that frame of reference. We have always had to apologize for India and now is the time we don't want to apologize for our country. We want to be proud of it.[1]

Kiran Mazumdar-Shaw

Biocon's Bangalore headquarters office was brimming with activity on the morning of April 27, 2009. That morning, Biocon's senior management was meeting to discuss its oral insulin, IN-105. Harish Iyer, head of research and development (R&D) at Biocon, and Anand Khedkar, senior scientific manager of the oral insulin project, were completing their final presentation to the committee about the progress of IN-105 and potential options for the future. The financial year 2008-2009 had turned out to be one of the most difficult years for Biocon, with all indications pointing to a sharp decline in post-tax profits amid a depressed global economy. However, Biocon's research endeavors, such as IN-105, were just beginning to deliver success, and the company was in the process of creating a global profile as a leading Indian innovator. The IN-105 concept was revolutionary yet risky. Early results from Phase II studies were getting favorable reviews from scientific experts in the United States and Europe. Biocon's management had to decide the next steps. The scientific advisory committee had recommended proceeding with Phase III studies, but the scale of the study — whether to have it within India or as a global study, or if it should be done with a partner or not —was not yet decided. Unlike many of Biocon's projects in the generics arena, this project would require a significant resource commitment, with very little guarantee of success. However, if successful, it would open up a substantial global opportunity for the company.

THE GLOBAL BIOPHARMACEUTICALS INDUSTRY

The global biopharmaceuticals industry generated revenues of US$615 billion in 2008, and had a compound annual growth rate (CAGR) of 4.7 per cent over the previous five years. The total industry revenue was expected to reach US$734 billion by 2013, with a CAGR of 3.6 per cent for the period 2008-

[1] *Vikas Pota, "Healing the World," India Inc.: How India's Top Ten Entrepreneurs are Winning Globally, Nicholas Brealey Publishing, 2010.*

2013.[2] The traditional pharmaceutical industry was based on the chemistry of specific active compounds characterized by small molecules, i.e., typically 20-100 atoms. They were manufactured using chemical reactions and analyzed using routine laboratory tests. In contrast, biotechnology firms were involved with molecular-biology-based compounds known as biologics that were significantly larger in size. For example, small biologics were composed of 200-3,000 atoms, while large ones varied from 5,000-50,000 atoms. Biologics were typically synthesized from a microorganism, plant or animal cells, and the properties of biologics were highly sensitive to the nature of the manufacturing process. The biotech sector alone had been growing at 10.2 per cent per annum from 2005 to 2009 and was expected to reach a value of US$318.4 billion by the end of 2014.[3] The biotechnology industry was mainly located in advanced economies. The United States topped the list with 1,750 firms compared to 824 in France, followed by 773 in South Korea, and 659 in Spain. India ranked 11th overall with 325 firms, and was ranked fourth in Asia-Pacific after South Korea, Japan and Australia.[4]

Drug development, from discovery to marketing, was estimated to require an investment of nearly US$1 billion, and industry profitability was under constant attack as costs continued to rise and prices came under pressure. Industry experts estimated that on average, only 25 truly novel drugs, termed within the industry as new chemical entities (NCEs), gained approval for marketing in any single year. This approval involved a heavy investment in pre-clinical development and clinical trials, as well as a commitment to ongoing safety monitoring.

The drug development process was long, often taking 10 to 15 years, going through the discovery phase (average three to six years), the preclinical testing phase (average one year), the clinical trial phase involving human patients (average six to seven years), and the regulatory approval phase (one year)[5] (see Exhibit 1). A company applied for a patent for a new chemical entity (NCE) or a production process for the drug, for which it got exclusive rights for 20 years from the date of application. It typically took seven to10 years after the discovery to test the compound in clinical trials before introducing it in the market. Once the patent expired, typically other competing firms made a generic drug version of the product. Development and approval of generics was less risky and inexpensive compared to the original drug, and generics typically were sold at one-tenth of the original drug price, if not less. Typical returns on investment for a generics manufacturer were approximately five to fifteen per cent. However, competition in this field was getting fierce with an increasing number of players and the globalization of the generics industry.[6] In some cases, the multinational companies were establishing wholly owned subsidiaries to produce and market generics, thus intensifying competition in the generics sector.

The Indian Context

The evolution of the pharmaceutical industry in India was punctuated with many policy shifts over the years. Post-independence India had no indigenous capabilities to produce pharmaceuticals, and largely depended on imports. The Patent and Designs Act of 1911, a legacy of the British colonial rule, enforced adherence to the international patent law and helped establish a number of foreign firms that preferred to import drugs from their respective countries. However, the Patents Act of 1970 abolished the product patents and permitted process patents only for five to seven years. The objective was to encourage the development of an indigenous pharmaceutical industry and to provide Indian consumers with low-cost

[2] *"Global Top 10 Pharmaceutical Companies," Datamonitor, 2009.*
[3] *"Global Pharmaceuticals, Biotechnology & Life Sciences," Datamonitor, March 2010.*
[4] *"India Life Sciences: Vision 2010," report prepared by Confederation of Indian Industry and Yes Bank.*
[5] *"Biotechnology in Asia-Pacific," Datamonitor, May 2010.*
[6] *http://pubs.acs.org/cen/coverstory/8013/8013genericdrugs.html, accessed December 2010.*

medicines. This encouraged local firms to make copies of drugs patented by firms in other countries, by unique manufacturing processes at relatively cheaper prices.

A sharp reduction in profitability and the risk of losing proprietary technology caused many multinational companies to opt out of India in the 1970s. However, the economic liberalization of the 1990s and India's entry into the World Trade Organization in 1995 brought back the patent regime and the openness to multinational investment. The WTO Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement required India to comply and grant a "product patent" to all new chemical entities (NCEs). A delay in implementation of the TRIPS Agreement until 2005 was done to enable the filing of patents beginning in 1995 in a "mailbox" format. Between 1995 and 2005, approximately 9,000 applications were filed.[7] By 2001, 100 per cent foreign ownership was permissible in the Indian pharmaceutical sector.

As drug development costs soared, global pharma companies started looking at emerging markets such as India and China, where pharmaceutical production costs were at least 50 per cent lower than in Western nations.[8] Clinical trials in markets such as India were estimated to cost 30-65 per cent of the costs in the United States or the European Union. Due to the large patient populations available in these countries, it was also easier to recruit patients, which in turn shortened drug development time.[9]

The new patent regime, coupled with the large pool of local talent and returning Indian diaspora with interest in establishing new ventures in India, was compelling many Indian companies to discovery-based research.[10] Although funding continued to be a major constraint, several Indian firms were adopting a hybrid model of straddling both discovery R&D and the generics business.[11] Kiran Mazumdar-Shaw, founder and CEO of Biocon, reflected:

> The Indian pharmaceutical sector in general has thrived on generics or me-too products. In the biotech industry, too, most companies are opting for bio-generics. In Biocon, we have balanced our portfolio between bio-generics and novel research programs. The talent you require for bio-generics is in no way inferior to novel research. Yes, you have to invest far more because you're doing something for the first time. The difference between bio-generics and novel research isn't so much about the talent as the management risk appetite.

While rapidly declining profitability in generics was a trigger for many Indian drug companies to foray into discovery research, the institutional environment in India posed several hurdles. Biopharmaceutical firms had a difficult time finding appropriate talent and/or risk capital, and also had a difficult time with an arcane regulatory system and lax enforcement of intellectual property rights. Every year India produced a million bachelor's degree holders, 150,000 master's degree holders, about 2,000 Ph.D. scientists in the life sciences, and close to 20,000 medical graduates. However, many business leaders felt that they were not well trained for the industry's needs. Mazumdar-Shaw commented:

> Finding good talent is a serious problem, particularly in the Biotech sector. There are a lot of potentially trainable people. When you look at the number of graduates the numbers

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[7] "Will the Lifeline of Affordable Medicines for Poor countries be Cut? Consequences of Medicines Patenting in India," February 2005, Médecins Sans Frontiéres Publication, www.who.int/hiv/amds/MSFopinion.pdf, accessed December 2010.
[8] "Indian Pharmaceutical Industry: Vision 2015," report prepared by OPPI and Yes Bank, 2008.
[9] "The Continuing Evolution of the Pharmaceutical Industry: Career Challenges and Opportunities," Regent Atlantic, April 2010.
[10] "UNESCO science report, 2010: The current status of science around the world," UNESCO, 2010.
[11] "Ranbaxy buyout heats up Indian M&A," Scrips News, December 2008; "Bridges that Indian Biosimilar Makers Must Cross to Prosper in International Markets," Genetic Engineering and Biotechnology News, August 7, 2009.

> sound very good. But, when you consider how many you can actually hire from that huge ecosystem, that's where the problem is. They are not skilled and not trained to do what the industry is looking for.[12]

Dr. Harish Iyer, Biocon's head of R&D, echoed those sentiments:

> I think we have an outstanding R&D group on par with the best in the world and who routinely interact with the best in the world. However, I am not able to hire enough people fast enough at a senior level to keep up with our needs. We have hired a lot of people from global companies. We continue to hire. But, it is still hard to find very experienced top notch professionals at the salaries we want to pay. It is a challenge, no doubt about it.

BIOCON HISTORY

Biocon was established by a Bangalore-born scientist turned entrepreneur, Kiran Mazumdar-Shaw, daughter of the chief master brewer and managing director of United Breweries in India, the maker of the famous "Kingfisher" beer. After earning her graduate degree in brewery from the University of Ballarat in Australia, Mazumdar-Shaw found it hard to get a brewery job in India, as the brewing profession was male-dominated at that time, so she set out to leverage her fermentation know-how with a small biotech outfit in her garage with just ₹10,000 as an investment.[13] In 1979, she formally registered the company as a joint venture with Biocon Biochemicals Ltd. of Ireland to manufacture and export enzymes to international markets. Unilever plc of the United Kingdom owned Biocon Biochemicals Ltd. of Ireland for a period, but in 1994, when Unilever divested the ownership, Indian promoters bought out the foreign shares, establishing Biocon as a wholly owned company. For much of its first two decades, Biocon remained an enzyme company and focused its in-house research programs on various fermentation technologies.

In 1994, seeing the need for outsourced R&D in multinational firms, Biocon set up India's first contract research company, Syngene, to conduct chemistry- and biology-related research in partnership with some of the world's biggest drug firms, such as Bristol-Meyer Squibb and Astra Zeneca. In 2000, Biocon launched another entity called Clingene to focus on clinical trials.[14]

In 2001, Biocon became the first Indian company approved by the U.S. Food and Drug Administration to produce the generic version of Mevacor (Lovastatin), a cholesterol drug. Subsequently, generic versions of other statin drugs, such as simvastatin and pravastatin, were also manufactured at Biocon. All these drugs were sold in North America using Genpharm, a Canadian company. By 2004, Biocon had 50 per cent of the U.S. market for generic statins.[15] Biocon's fermentation competence was particularly helpful in its entry into the insulin market, which was then dominated by two global giants, Eli Lilly and Novo Nordisk. In 2003, Biocon introduced Insugen, its brand of insulin priced at 25 per cent below market, a luxury afforded by the low development costs in India. Within a year, Insugen was able to secure a 10 per cent market share in India. In 2004, it entered into an agreement with Bristol-Meyer Squibb as part of a nine-year supply of the recombinant human insulin.

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[12] http://knowledge.wharton.upenn.edu/india/article.cfm?articleid=4144#, accessed December 2010.
[13] The symbol ₹ denotes Indian rupees. Average currency value for 2009 (₹/USD): ₹46.55 = US$1.
[14] Company reports, 2010.
[15] "Big Shot in Bangalore," Forbes, October 18, 2004.

Biocon was listed in the Bombay Stock Exchange in 2004, and on the day of listing and the initial public offering (IPO) it was oversubscribed 32 times, crossing US$1.1 billion. In 2008, Biocon divested its enzyme business to a Danish firm and set up a wholly owned subsidiary in Switzerland, Biocon SA, which in turn acquired 71 per cent equity interest in Germany-based AxiCorp, which was primarily a pharmaceutical distributor business in Europe. In February 2009, Biocon SA raised the stakes to 78 per cent. Biocon believed that the marketing and distribution network in Europe would serve it well for its launch of insulin products in the European market.[16] As of 2009, Biocon was the number 1 biotech firm in India with global sales of US$712 million in more than 75 countries. Its product portfolio consisted of 36 key brands across the four therapeutic divisions of diabetes, nephrology, oncology, and cardiology (see Exhibit 2).

Biocon prided itself on its entrepreneurial culture that encouraged open communication and attracted top talent in the field, both from highly reputed Indian institutions and individuals returning from abroad. Mazumdar-Shaw was meticulous in listening to her employees and involving them in building her company's vision. She consciously fostered an informal atmosphere where employees were encouraged to speak their minds without fear of displeasing their boss. By engaging with employees at every level, she ensured that Biocon did not have a feudal structure.[17]

Shifting R&D Focus to High-risk Innovation

Biocon's R&D programs were financed mainly from internal accruals and stood at 7.5 per cent of Biocon's standalone revenue. The experience in the late 1990s and the early 2000s with statins and insulin gave the company a competitive edge in process technology, as well as the capacity to analyze and manage risk. The company's manufacturing capability brought in significant cash flow, which was reinvested in building research competencies. Unlike most Indian companies, Biocon focused on building intellectual property. For example, Biocon filed several patents for its solid-state fermentation technology, which set Biocon on the path to do things differently from other generic drug makers in India.

Dr. Iyer had worked for Genentech and Biogen-IDEC prior to joining Biocon in 2001. He was a chemical engineering graduate from the Indian Institute of Technology, Madras, and a doctorate from the prestigious Rensselaer Polytechnic Institute in the United States. He was appointed head of R&D in 2007. Iyer recalled Biocon's shifting emphasis toward discovery-driven research:

> At Biocon, we did not start with a focus on research in the beginning. We started from day one as a commercial organization. We started as a manufacturing company. We did research but the research was somewhat on a small scale and we did not have VC funding such as companies like Genentech to. There is a big difference from a biotech company that has been doing research for several years making no money but believing that it can do well, while Genentech comes with a different culture. We sort of started with some emphasis on research but maintaining sales, making sure we could create enough revenue was a big part of our culture. So the way we have grown as a company, you have to keep this at the back of your mind at all points in time. We have been profitable from day one.

In 2005, despite a flourishing and lucrative generics manufacturing business, Biocon decided to shift its focus to more innovative products. Iyer recalled:

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[16] *"Biocon Injects Innovation Gene," Technology Review, MIT, October 2009.*

[17] *Vikas Pota, India Inc.: How India's Top Ten Entrepreneurs are Winning Globally, Nicholas Brealey Publishing, 2010.*

> There was a great deal of interest in the company that we should be doing something innovative and different. The reason for that was quite simple. If you continue in the same business that you are in, you will die because there is so much competition out there. The cost of manufacturing keeps coming down, your margins will keep coming down, there is not that much of a technology barrier to get into these fields. From a business perspective it does not make sense to be in this game where everybody is going to beat you in the end.

As of 2009, Biocon's research pipeline included BIOMAb T1h, an anti-CD6 monoclonal antibody for the treatment of psoriasis; BVX20, an anti-CD20 to treat cancer, inflammation, and autoimmune disease; and novel peptides developed in collaboration with Amylin (see Exhibit 3). The case of BIOMAb was illustrative. In 2005, Biocon started a research program targeted at head and neck cancer, along with a Cuban research institution, the Centre of Molecular Immunology (CIMAB), which had developed monoclonal antibodies (MAbs) that could specifically target cancer cells and could also be extended to treat autoimmune diseases like rheumatoid arthritis and psoriasis. Iyer commented:

> Cuba is not a rich country by any stretch of the imagination. Certainly India is also not a rich country but there are people in India who are richer than people in Cuba. How they do fundamental research in the south and through that research come up with even one product is an astonishing feat. With CIMAB, we have come across several such products in our interactions with them. We have got at least two or three in the pipeline now. So that is a very big deal when you are talking about companies struggling to find even one product.

Mazumdar-Shaw's leadership was critical for the focus on research, and despite being located in India, an emerging economy, Biocon had established itself as a global firm. Iyer continued:

> Kiran played a strong role for research in terms of long-term risk taking, which is what a company like Genentech bets on. A start-up biotech company says, "I will bet on high-risk projects that have a ten-year horizon and 10 to 20 per cent chances of success if at all." That is high long-term risk. We are not a capital-rich society. For years, we have been relatively risk averse in this business. So that takes time. For example, oral insulin is at least a five- to ten-year horizon before we can see anything coming out of it. If I make Simvastatin (a generic drug) I can expect returns in a year or two maybe. And so why would you ever pursue something that is longer term, bigger picture and the odds are completely stacked against you? That's a leadership call.

The balanced approach to risk characterized the Biocon way. Given its success in insulin manufacturing, Biocon was actively exploring options in insulin research.

DIABETES TREATMENT

Diabetes is a disease marked by high levels of blood glucose resulting from defects in insulin production or action, or both. Insulin is a hormone secreted by the pancreas, which increases the ability of tissues to absorb blood glucose. It is also the principal hormone that regulates uptake of glucose from the blood into most cells. Diabetes can lead to serious complications and premature death, but people with diabetes can take steps to control the disease and lower the risk of complications.[18]

[18] *"National Diabetes Fact Sheet, 2007," Center for Disease Control, 2007.*

Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, which are involved in making the hormone insulin, which regulates blood glucose. Type 1 diabetic patients need injectable insulin to survive. Type 2 diabetes is non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. In adults, Type 2 diabetes accounts for about 90-95 per cent of all diagnosed cases of diabetes and typically develops in middle age. Type 2 diabetes is associated with older age, obesity, family history of diabetes, and several other factors.

In 2009, 6.4 per cent of adults around the world, or 285 million, had diabetes; by 2030, the prevalence of diabetes was expected to increase to 7.7 per cent, or 439 million adults. It was anticipated that there would be a 69 per cent increase in diabetes in developing countries and a 20 per cent increase in developed countries between 2010 and 2030. As of 2009, India topped the list of countries for the largest number of people with diabetes, estimated at more than 50 million, and expected to reach 87 million by 2030. Global expenditures on diabetes were expected to reach half a trillion U.S. dollars by 2030[19] (see Exhibit 4).

The discovery of insulin made from a bovarian pancreas in 1922 made treating diabetes possible. Genentech, a biotechnology firm, discovered a process in 1978 for synthesizing human insulin and producing it in large volumes. Later in 1982, Eli Lilly introduced genetically engineered human insulin using a bacteria-induced process. In 1988, Novo Nordisk, a Danish firm, developed a yeast-based process for manufacturing insulin. By the 1990s, recombinant human insulin had emerged as the norm for diabetes treatment, and Eli Lilly and Novo Nordisk together held a 90 per cent share of the global insulin market. The US$12.3 billion insulin market was quite diverse and was constituted by a range of insulin types (see Exhibit 4).

Mazumdar-Shaw reflected:

> India is the world's capital in diabetes. We have 1/4th of the world's diabetics in India. Of 140 million diabetics that are estimated in the world, India accounts for 40 million of them. In India the form of diabetes is not linked to lifestyle. There is a genetic predisposition that Indians have towards diabetes. Adding to that is India's growing affluence, affecting India the same way as affluence is affecting U.S. Diabetes is a growing pandemic and still there are unmet needs. It's a very crowded area especially if you look at the research focus. Every single pharma company and a lot of biotech companies are looking at diabetes as the sector where the next big blockbuster activity is. We as a company have a very robust technology.[20]

ORAL INSULIN RESEARCH AT BIOCON

Injectable insulin was a fast-acting drug delivery method. However, patient compliance was sometimes very poor due to the inconvenience of its administration. Also, injected insulin entered the bloodstream and resulted in fat and muscle being exposed to higher insulin, which caused weight gain and other side effects. The introduction of pump devices and prefilled pens made insulin administration simpler and more convenient, and the introduction of oral and inhaled insulin would make drug delivery even more convenient and help in improving patient compliance as well as controlling glycemic better.[21] Insulin

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[19] *www.hopkinsguides.com/hopkins/ub/view/Johns_Hopkins_Diabetes_Guide/547049/all/Epidemiology_of_Type_2_Diabetes, accessed December 2010.*
[20] *http://knowledge.wharton.upenn.edu/india/article.cfm?articleid=4144#, accessed December 2010.*
[21] *"The Diabetes Market Outlook to 2014," Business Insights, 2009.*

taken orally was directed toward the liver, which was more effective in controlling increased glucose levels after meals.[22]

Anand Khedkar, project manager for the oral insulin program, joined Biocon in 1997 after receiving his graduate degree in pharmacy from UDCT (University Institute of Chemical Technology), India's premier institute for chemical technology. Khedkar joined Biocon at a time when the company was shifting its focus from enzymes to biopharmaceuticals. Khedkar recalled:

> I had read a lot about oral insulin and I was keen to work on that idea as we did not have any formal program at Biocon. I went and talked to our then head of R&D, Dr. Shrikumar Suryanarayan, and asked him if he would let me study the delivery mechanisms of oral insulin in animal models. It was not a big financial commitment but he was enthusiastic about it and gave me the go ahead for the study.

That was in 2002. Within a year, Khedkar had data that supported his conjecture that oral insulin could potentially work. Khedkar recalled:

> At that time, there were many conjectures on the feasibility of oral insulin. What we had was solid data that supported that in animal models. To me, that was great excitement. And that got me to push the idea even more. We had the proof of concept that glucose values can come down when oral insulin is administered with the right technology. Added to that was the fact that we already had the know-how to make insulin in a cost-effective manner.

In 2004, Mazumdar-Shaw attended an American Diabetes Association conference and the presentation of a research team from Nobex, a North Carolina-based biotechnology firm which had promising data on an oral insulin molecule, HIM-2. Nobex had signed a licensing deal with GlaxoSmithKline (GSK), which was worth about US$283 million in June 2003, to develop one of its oral insulin molecules as a companion to Avandia, GSK's blockbuster diabetes drug. But in November 2003, GSK decided to abandon the project for unspecified reasons. Nobex had gone back to the lab and had come up with a new insulin molecule, HIM-2, that was more potent and could be absorbed more easily. Within months, Biocon and Nobex signed a formal agreement to collaborate on the HIM-2 program, with Biocon investing about US$6 million. The two companies agreed also to co-develop two experimental drugs, the insulin pill and a pill to treat cardiovascular disease. Neither drug had been tested on humans.

Unable to survive after the GSK pullback, Nobex filed for bankruptcy in 2005. Biocon made a strategic decision to acquire the company's intellectual property for US$3.5 million and start an in-house research program leveraging the data.[23] Khedkar and his team worked to refine the formulation based on available data and developed a newer version of the formulation for clinical study, and the IN-105 program was born. The second-generation oral insulin, IN-105, was developed at Biocon and proved to perform better than HIM-2.[24] Mazumdar-Shaw recalled:

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[22] C.A. DiCostanzo et al., "Simulated first-phase insulin release using Humulin or insulin analog HIM2 is associated with prolonged improvement in postprandial glycemia," Am. J. Physiol. Endocrinol. Metab, 289, 2005, E46-52; N. Dave et al., "Process and purification for manufacture of a modified insulin intended for oral delivery," Journal of Chromatography A, 1177, 2008, pp. 282-286.

[23] www.redorbit.com/news/health/324227/drug_developer_nobex_files_for_bankruptcy_seeks_buyer, accessed December 2010.

[24] Company reports, 2008.

> We believed that we had some advantage to focus on the oral insulin research program. For a program like this, the cost of goods is a major factor to be able to have commercial success. Our location, India, was a huge advantage for us in this. We can actually bring commercially viable oral insulin into the world market. Oral insulin would have a unique therapeutic effect as compared to plain insulin because of the way it is delivered. I really believed that it had the potential of reversing early-stage diabetes.[25]

Biocon's IN-105 was considered one of the oral insulin programs furthest along in its development. Of the active oral insulin programs, industry experts looked at four companies besides Biocon: Emisphere (United States), Diabetology (United Kingdom), Diasome (United States), and Oramed (Israel) (see Exhibit 5 for an overview). A number of companies had attempted oral insulin formulations. Autoimmune Inc., a California-based biopharmaceutical company, had developed an oral insulin formulation (AI-401) and partnered with Eli Lilly and the National Institute of Health for a Phase III trial, which was abandoned after several years, and the company had filed for bankruptcy. Pfizer had developed an inhalable insulin, branded as Exubera, which was approved by the FDA in January 2006. However, due to a number of reported side effects, Pfizer pulled the drug off the market in October 2007. Biosante, Coremed, Cortecs, Eligen, Nobex, and Protein Delivery were some of the companies that had attempted to develop oral insulin but failed.

CHALLENGES FACING IN-105/FUTURE OF IN-105

Biocon had come a long way since 2003, when it first moved toward the idea of discovery research and initiated its oral insulin project. The success of BioMab EFGR for cancer treatment was a great encouragement. Now, the overwhelmingly positive data from Phase II studies in India from IN-105 called for a deeper move to Phase III, a high-risk project. While the company had shied away from overly aggressive moves, it had consistently moved ahead in its quest to establish itself as an innovation leader. As the management committee was meeting to finalize its strategy for IN-105, Iyer and Khedkar were anticipating that three major issues specific to IN-105 would be raised at the meeting: Should Biocon undertake this risky investment now? Should the clinical trial be local or global? And should Biocon go with a partner or go it alone? The company also anticipated that the discussion would likely go beyond IN-105 to a broader discussion of Biocon's R&D strategy (see Exhibit 6).

(1) Should Biocon undertake this risky investment now?

While advancing through the Phase I and Phase II stages for IN-105 had not posed major issues, the Phase III decision was generally seen by the management as a critical decision. The financial situation in 2009 added another layer of difficulty: whether to commit a significant amount to what would be seen by the investor community as a high-risk project. M.B. Chinappa, Biocon's vice-president of finance, said on concerns at the time about the decision to go into Phase III:

> We look at it from a smaller biotech perspective. Do our balance sheet and our P&L support taking a significant risk in the global environment? Once you are committing the money, if things go wrong then the impact of all that money going away is significant. So you try to balance it in some way. When I am putting that money into a global study, I want to ensure that my probability of success is very high. A big pharma can spend US$50 million, and if things go wrong, it may not matter much. It is not their entire year's

[25] *http://knowledge.wharton.upenn.edu/india/article.cfm?articleid=4144#, accessed December 2010.*

> profit. However, for Biocon the case is very different. Although we would like to place bigger bets, at the end of the day we owe it to the shareholders. We owe it to the general public that we will manage their money prudently. Basically, you have to manage your risks such that if anything goes wrong, the company is still alive and kicking on all counts. But at the same time knowing that these are the things that will give you significant value and grow your company in the longer term.

The decision to advance to Phase III, the most expensive phase of the clinical trials, was indeed critical, coming at a time when the company had just gone through one of its most difficult years financially due to the global recession. Also, several Indian pharma companies which had ventured into discovery research were not seeing positive results and were cutting back on their research commitments. In 2008, following several setbacks in its clinical trials, Dr Reddys Laboratories (DRL) removed the words "discovery led global pharmaceutical company" from its vision statement, in a dramatic move, and shut down its R&D subsidiary, Perlecan Pharma, which it had started three years earlier in partnership with Citibank and ICICI Venture with a mission to drive high R&D. Glenmark, another Indian pharma company which had several molecules licensed to Merck and Eli Lilly in 2006, was going through a difficult period as both the alliances were being terminated in 2008 due to problems that had emerged during clinical trials.

Overall, there was consensus that IN-105 had potential. However, the challenges associated with the molecule were not trivial. Would Biocon be able to develop and manufacture it at a lower cost and meet the price point at which it could become a marketable item? Many within the organization felt that whether to go to Phase III or not was not the question. Since Biocon had had a successful Phase II study, the logical next step was to continue on with Phase III. But the exact way to go about it was what required deliberation.

(2) Should the clinical trials be done locally or globally?

Although the Phase I and Phase II clinical trials for IN-105 were done in India, moving to Phase III in India had its own advantages and risks. Patient recruitment was three times faster in India, saving 68 per cent of the required time compared to the United States[26] (see Exhibit 1). Regulatory norms in India required fewer patients (~500) for Phase III trials, compared to 1,000-5,000 in the United States. While doing a global trial would require a longer approval time and would be a more expensive proposition, the global market outside India was substantial and reaching that segment would not be possible otherwise. Anand commented on the value of doing a clinical trial in India versus the United States:

> In India, Phase III trials will cost you 2.2-2.7 million U.S. dollars with 500 patients. While in U.S.A., 500-patient clinical trial constitutes Phase IIa/III clinical trial. Some elements of efficacy are studied but largely it's a safety study. If we do the trials in India, although we take a risk, we also reduce the magnitude of the risk.

Chinappa, on the cost of doing a large study versus a small study:

> The actual cost is incurred by the hospitals — cost of administrations, hospital and doctor. If you go up from 100 to 200 patients and double the number of investigations and double the number of hospital sites, the costs increase too. It is about US$10,000 per patient for non-oncology trials and about US$20,000-25,000 for slightly standard trials. So going

[26] *"Booming Clinical Trials Market in India," RNCOS Online Business Research, November 2007, www.canbiotech.com/CommonData/NewsFiles/Booming%20Clinical%20Trials%20Market%20in%20India.pdf.*

> from 200 to 800 patients is like going from US$2 million to 8 million. During that early phase we create an infrastructure to make a limited amount of drug for testing. For IN-105 we were lucky because we already had facilities to manufacture insulin.

(3) Should Biocon go with a partner or go alone?

Most companies at this stage would seek a large pharmaceutical firm to provide an infusion of capital as well as to guide them through the critical stages of trials and managing the regulatory approval process (e.g., Nobex with GSK). The patent for IN-105 was filed in 2005, which gave Biocon patent protection for oral insulin for 20 years. The competitive dynamics of the other players also vying for a product on the market put phenomenal pressure on getting the drug to market at the earliest. Working with a global partner with deep pockets would not only ensure faster clinical trials on a global scale but would also provide the much-needed infusion of cash. However, the scientific team felt that there was a strong likelihood that Phase III results would come out in support of the drug, which would substantially elevate the valuation of the molecule. Khedkar commented:

> If you want to look for a global partner, you have to think how much value they would add at this particular time? If we go for a deal after a long-term study establishing efficacy and safety issues, the valuation would be very different compared to now. Typically in pharma, the deal value is 7-12 per cent up front of the total deal but the value one would get at this stage would be much smaller. Valuations increase exponentially along the development curve. But, it is also a judgment call. Today the value of my drug could be small but with every step I take there is a very high chance of failure. There is real risk that you may be diminishing the value if you get negative results.
>
> From another perspective, when you consider the speed, it may have a very different implication. A global player, once it has the proof of concept, typically does multiple clinical studies in parallel. Speed is everything. Every year you delay you are eroding peak sales value. By waiting for the results, one could ask if we are delaying the time to market. Partnering may be one way of de-risking to the extent that it adds value to the product and increases the probability of success.

IN-105 Strategy Meeting Agenda

The management meeting's agenda for the day focused on the IN-105 strategy. Overall, the oral insulin research had moved smoothly without many problems up to that point. Phase III, with a significant budget and high risk, was already drawing substantial attention from the analyst community, as well as the media. Iyer and Khedkar were convinced of the move forward. Khedkar remarked:

> For over a hundred years no one has been able to change the way insulin is administered. If Biocon is able to do it, then it completely changes the way diabetes is treated. Even if we fail, each step would be a learning process for Biocon's long-term R&D capabilities.

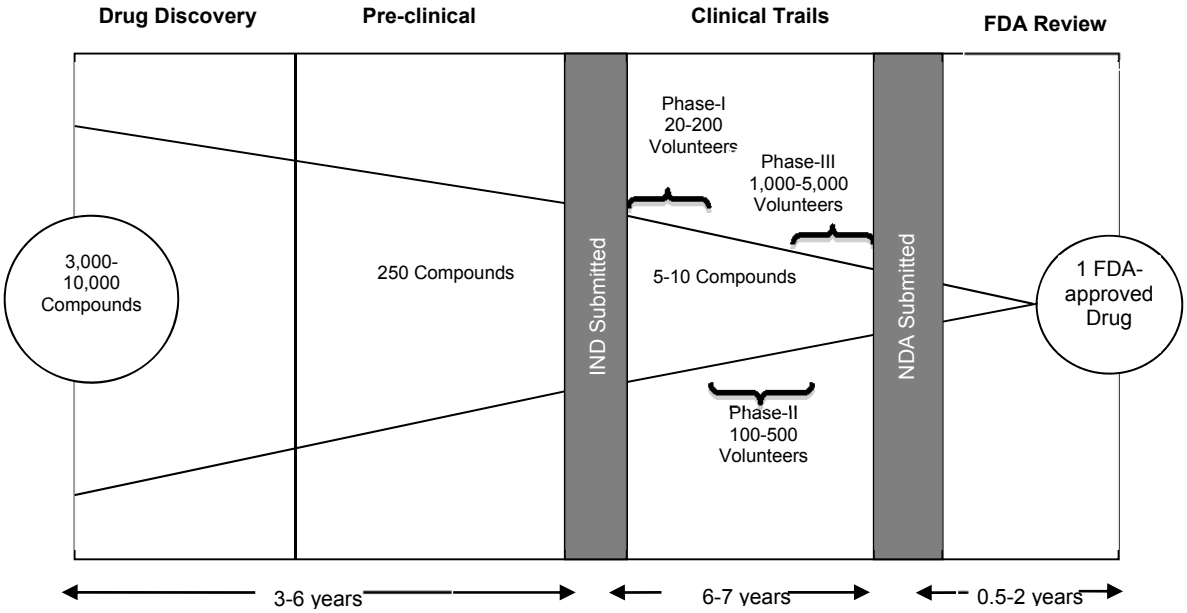
The IN-105 project decision brought into focus Biocon's overall innovation portfolio and its R&D strategy. Mazumdar-Shaw's opening statement at the meeting summarized her posture:

After the global downturn in 2008, the economy is now showing signs of recovery. Nevertheless, market dynamics continue to be unpredictable the world over. It is prudent at a time like this to remain committed to our innovation-led business strategy, which we believe will enable us to build a strong competitive edge for the foreseeable future. Innovation empowers us with the ability to develop market leadership through proprietary products and processes that can effectively counter the threat of commoditization and diminishing returns that most generics face. Innovation, we firmly believe, holds the key to leadership and profitability.[27]

[27] *Company report, 2009*.

Exhibit 1

DRUG DEVELOPMENT PROCESS



	Stages of clinical trials[1]	Mean U.S. cost with St. Dev[2] (in mil US$)	Indian cost[3]
Phase I	Clinical trials are the first evaluations to determine the safety, dosage range, or side effects of new drugs or treatments. Patient group size 20-200.	15.2 ± 12.8	50% less than average cost in U.S.
Phase II	Clinical trials test the drug or treatments among a larger group of patients (100-500).	23.5 ± 22.1	60% less than average cost in U.S.
Phase III	Phase III trials are used to confirm effectiveness, monitor side effects, and compare the drug or treatment to commonly used treatments. Patient group size 1,000-5,000.	86.5 ± 60.6	60% less than average cost in U.S.

Percentage probability of success for each phase[4]

	All Drugs	Big Pharma	Small Pharma	Biologics	Chemicals	Diabetes Drugs
Phase I	81	73	82	90	84	86
Phase II	57	50	59	67	66	65
Phase III	57	69	54	70	66	89
Cumulative	26	25	26	42	37	50

Source: "The Continuing Evolution of the Pharmaceutical Industry: Career Challenges and Opportunities," Regent Atlantic, April 2010.

[1] *"Industry Insight — Clinical Trials in India," Cygnus Business Consulting & Research Pvt. Ltd., February 2010.*
[2] *J.A. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," Journal of Health Economics, 22:2, March 2003, pp. 151-185.*
[3] *Institute of Clinical Research, India.*
[4] *"Pharmaceutical Development Phases: A Duration Analysis," Bureau of Economics, Federal Trade Commission, www.ftc.gov/be/workpapers/wp274.pdf; C. Adams and V. Brantner, "Spending on New Drug Development," Health Economics, 19:2, February 2010, pp. 130-141.*

Exhibit 2

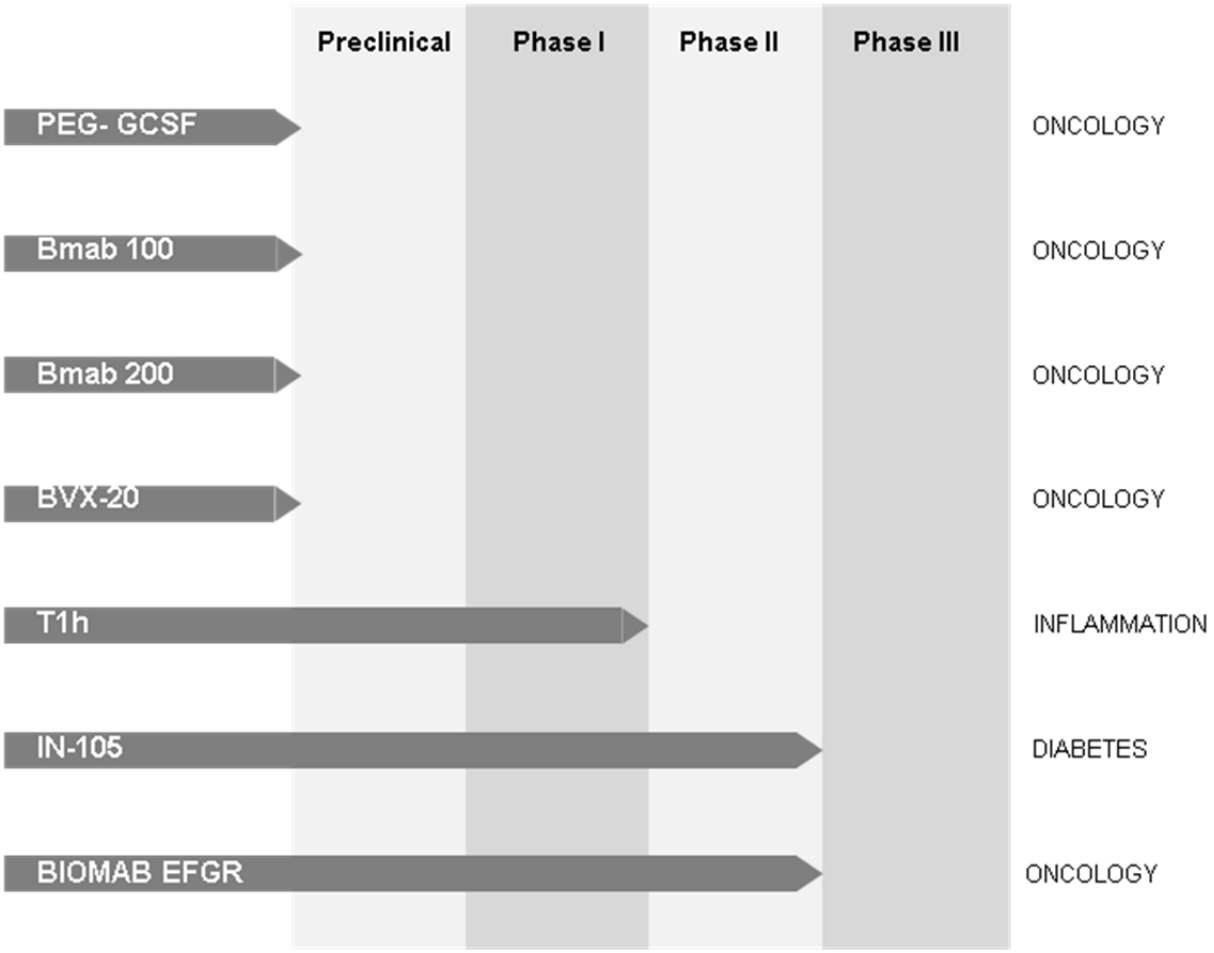
BIOCON LTD FINANCIAL DATA
(Amounts in Crores Indian Rupees)

Financial Year (ending March 31)	**2009**	**2008**	**2007**	**2006**	**2005**
Revenue by Segment					
Revenue from Pharma	1,384	832	742	602	556
Revenue from Enzymes	-	46	109	85	90
Revenue from Custom Research	225	176	135	101	66
Total Revenue	**1,673**	**1,090**	**990**	**793**	**728**
Revenue by Company					
Biocon	963	912	849	689	661
Syngene	206	160	132	98	66
Clinigene	21	18	9	6	1
Axicorp	480	-	-	-	-
Biocon SA	3	-	-	-	-
Research & Development Expenses					
Revenue Expenses	60	47	39	20	14
Capital Expenses	15	18	10	21	10
R&D as % of Revenue (Biocon)	7.8%	7.1%	5.8%	6%	3.6%
Profit before Interest, Depreciation and Taxes	387	342	287	234	239
Profit before Taxes	260	231	211	202	215
Profit after Taxes	**240**	**225**	**200**	**174**	**197**
Equity	1,511	1,484	1,069	888	741
Debt	524	255	187	105	76
Book Value per Share	70.5	71.7	50.9	41.9	34.5
Average Currency Value for Year (`/USD)	46.55	48.54	39.36	44.50	45.90

Note: ₹crore equals 10 million Indian rupees.
Source: Company reports.

Exhibit 3

BIOCON BIOLOGICS R&D PIPELINE (AS OF MARCH 31, 2009)



Notes:
PEG-GCSF, or granulocyte colony stimulating factor, is used to stimulate white blood cell production after chemotherapy.
Bmab100, a potential anti-cancer drug, targets the vascular endothetial growth factor (VEGF), while Bmab200 targets the epidermal growth factor receptor (EGFR).
BVX20 is a novel human monocloncal antibody that binds to CD20 and is potentially used to treat non-Hodgkin's lymphoma.
T1h is an anti-CD20 novel antibody to treat rheumatoid arthritis.
BIOMAB EFGR is a humanized monoclonal antibody used to treat head and neck cancers.
Source: Company documents.

Exhibit 4

DISTRIBUTION OF GLOBAL DIABETES MARKET 2007-2008

Drug Class	Leading Companies	Sales 2008 ($m)	Sales Growth 2007-08 (%)	Market Share 2008 (%)
Insulin Market				
Human Insulin	Novo-Nordisk, Eli Lilly, Sanofi-Aventis	12,278	19.7	44.9
Animal Insulin	Eli Lilly	5	4.7	0.1
Total: Insulin		**12,294**	**19.7**	**45**
Drug Targeting Underlying Causes				
Glitizone	Takeda, GSK, Bilim, Bio-Farma, Srovel, Cobalt Pharma	6,217	-7.9	22.8
Sulfonylurea	Sanofi Aventis, Servier, Mylan, Teva	2,001	2.7	7.3
Biguanide	Bristol Meyer-Squibb, Teva, Merck, Mylan, Menarini	1,954	5.9	7.2
DPP-IV	Merck, Novartis, Menarini	1,725	145.5	6.3
Alpha-glucosidase Inhibitor	Takeda, Bayer, Sanwa Kagaku Kenky	1,057	11.9	3.9
GLP-1	Eli Lilly/Amylin	700	19.8	2.6
Glinide	Novo Nordisk, Eurimpharm, Kissei Yakuhin, Daiichi Sankyo	812	12.7	2.9
Total: Drugs Targeting Underlying Causes		**14,465**	**7.2**	**53**
Other Anti-diabetics		**395**	**16.6**	**1.5**
Insulin Devices (Syringes, Insulin Pens, Pumps)	Novo-Nordisk, etc.	140	19.2	0.5
Total: Diabetes Market		**27,294**	**12.7**	**100**

Source: "The Diabetes Market Outlook to 2014," Business Insights, 2009.

Exhibit 5

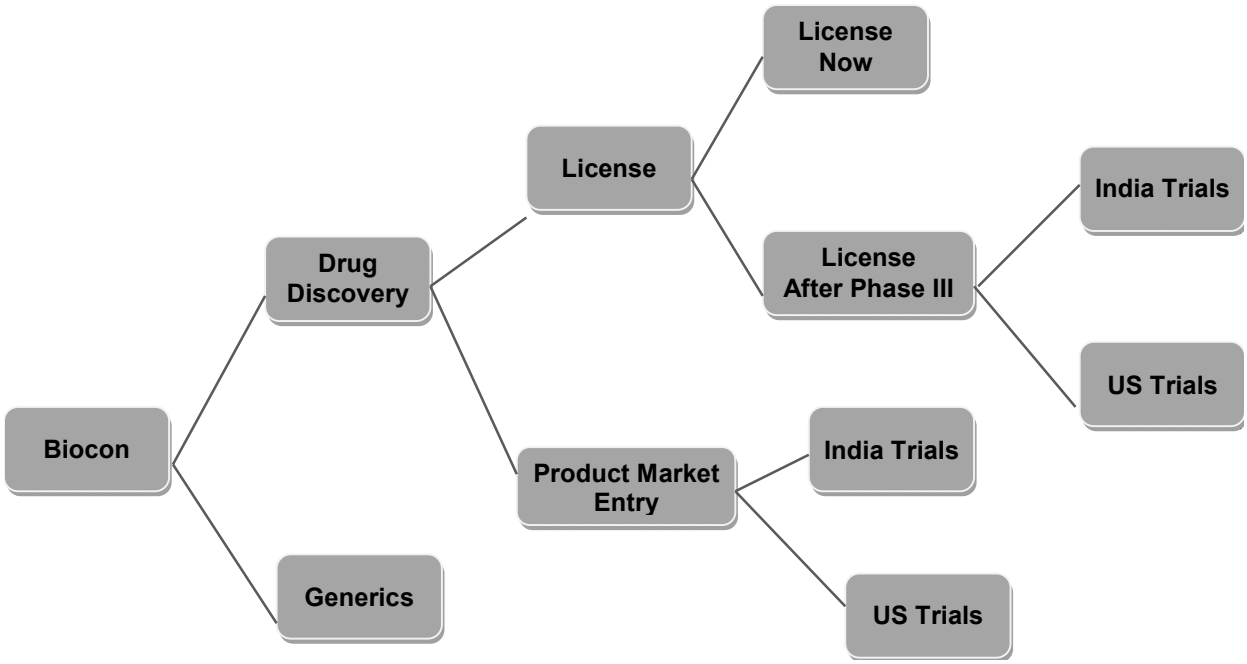
ORAL INSULIN ALTERNATIVES

Company	Product	Technology	Formulation	Last Reported Stage of Development (2009)
Access Pharmaceuticals	Cobalamin-based Insulin	Nanoparticle Vitamin B-12	NA	Preclinical
Biocon	IN-105	PEGylation plus Permeation Enhancer (PE)	Tablet	Phase II
Diabetology	Capsulin	PE	Capsule	Phase II
Diasome Pharmaceutical	HDV-I	Hepatic-directed Vesicles Insulin (HDV-I)	Tablet	Phase II
Emisphere Technologies	Eligen™	Eligen Carrier Technology plus Permeation Enhancers	Tablet	Phase II
Merrion PharmaCeuticals	NN1952	GIPET Enhancer	NA	Phase I
NOD Pharmaceuticals	Nodlin	PEGylation plus PE	Liquid	Phase I Abandoned
Oramed Pharmacueticals	ORMD-0801	Enteric Coating plus PE	Capsule	Phase I
Transgene Biotek	Unnamed	Polymeric Nanoparticles	NA	Preclinical

Source: "Nicer than Needles," Chemical & Engineering News, 88:22, May 31, 2010, pp. 27-30; "Oral insulin — a review of current status," Diabetes, Obesity and Metabolism, 12:3, 2010, pp. 179-185.

Exhibit 6

DECISION TREE



Source:Created by author.